BONE SARCOMAS LINKED TO RADIOTHERAPY AND CHEMOTHERAPY IN CHILDREN

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Abstract We estimated the risk of subsequent bone cancer among 9170 patients who had survived two or more years after the diagnosis of a cancer in childhood.

As compared with the general population, the patients had a relative risk of 133 (95 percent confidence interval, 98 to 176) and a mean (±SE) 20-year cumulative risk of 2.8±0.7 percent. Detailed data on treatment were obtained on 64 patients in whom bone cancer developed after childhood cancer. As compared with 209 matched controls who had survived cancer in childhood but who did not have bone cancer later, patients who had had radiation therapy had a 2.7-fold risk (95 percent confidence interval, 1.0 to 7.7) and a sharp dose–response gradient reaching a 40-fold risk after doses to the bone of more than 6000 rad. The relative dose–response effect among patients who had been treated for retinoblastoma resembled that among patients with all other types of initial tumors, although the cumulative risk of bone cancer in the retinoblastoma group was higher. Similar numbers of patients were treated with orthovoltage and megavoltage; the patterns of risk among categories of doses did not differ according to the type of voltage. After adjustment for radiation therapy, treatment with alkylating agents was also linked to bone cancer (relative risk, 4.7; 95 percent confidence interval, 1.0 to 22.3), with the risk increasing as cumulative drug exposure rose.

We conclude that both radiotherapy and chemotherapy with alkylating agents for childhood cancer increase the subsequent risk of bone cancer. (N Engl J Med 1987; 317:588-93.)

IONIZING radiation has long been known to induce bone cancers. In 1929 Martland observed bone sarcomas among workers painting radium on watch dials,[1] and the relation of bone cancers to the use of various bone-seeking radioisotopes is now well documented.[2] Therapeutic external beam radiation was convincingly linked to bone sarcomas in 1948,[3,4] but even today few quantitative data exist. In recent surveys, radiation risks have seemed especially high among patients treated at a young age, notably for retinoblastoma, Ewing's sarcoma, or Hodgkin's disease.[4-12] Bone cancers have also occurred after lower doses of radiation were given in childhood for nonmalignant diseases such as tinea capitis.[13] Treatment with cyclophosphamide, usually combined with radiation therapy, may increase the rate of second tumors in patients with genetic retinoblastoma or Ewing's sarcoma.[8,11] Few studies, however, have estimated the actual dose of radiation delivered to the site where bone cancer originated, or have quantified the effect of

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chemotherapy. We therefore undertook a study of childhood cancer to clarify the effects of radiotherapy and chemotherapy in inducing bone cancers.

Methods

Cohort Analysis

A roster was constructed that consisted of 9170 patients who had survived cancer in childhood for two years or more, from the records of 13 medical centers participating in the Late Effects Study Group.[14] Any patients with bone cancer diagnosed less than two years after the initial cancer were excluded because the latter cancer was unlikely to be treatment-related. Sixteen of 64 patients with secondary bone cancer were excluded from the cohort analysis because their first tumor had not been treated at a Study Group hospital. The period at risk for the development of bone cancer began two years after the diagnosis of the initial tumor and ended with the date of death, the date of last follow-up evaluation, or the date of diagnosis of bone cancer, whichever occurred first.

Rates of bone cancer specific for sex, age, and calendar year were obtained from the Connecticut Tumor Registry and applied to the appropriate number of person-years of observation in order to estimate the number of cases expected, as if the rates for the Connecticut population applied to our study population.[15,16] The incidence rates for Connecticut were used because the registry had been compiled over the years covered by the study and because the risk of childhood cancer varies little among Western countries.[17]

Tests of significance and confidence intervals for the relative risk (the ratio of observed to expected cases) were calculated by using exact Poisson probabilities. To determine the absolute risk, or excess cases of bone cancer per 10,000 persons per year, the expected number of cases was subtracted from the number observed; the difference was divided by the number of person-years of observation and then multiplied by 10^4. Cumulative probabilities that bone cancer would develop over time were estimated with the method of Kaplan and Meier.[18]

Case–Control Analysis

For each of the 64 patients with bone cancer, at least two patients without any subsequent neoplasm (a total of 209) were randomly selected as controls, matched according to the histologic characteristics of the first tumor, duration of follow-up (at least as long as the interval between the diagnosis of the initial tumor and that of bone cancer), age at the diagnosis of the first tumor (±2 years), sex, and race. At least one control was matched for the calendar year of diagnosis (±2 years), and at least one was not. Patients with retinoblastoma were matched according to whether the tumor was bilateral, when possible; 1 of 22 cases and 13 of 69 controls had unilateral retinoblastoma.

The diagnoses of the cases and controls were determined from pathology reports. A panel of Study Group pathologists confirmed the histologic findings on all first and second tumors of the cases. For all study subjects, detailed medical and treatment histories were abstracted from medical records. All data on radiotherapy and chemotherapy were collected up to the point of the development of bone cancer in each case, or the corresponding interval for each matched control.

Comparisons between the cases and matched controls were made by the conditional logistic-regression method and took into account variable matching ratios.[19] The dose of radiation to the site of the bone cancer and the amount of chemotherapy were categorized according to the overall distribution of cases and controls, and relative risks were calculated between each category and a referent (lowest-dose) category. Tests for trend were performed by designating the midpoint of each dose category as the representative value or score. Whenever the matching factors were not correlated with the exposure histories of the cases and controls, or the numbers of subjects were so small that the conditions necessary for regression analyses were not present, unmatched analyses were conducted.[20]

Radiation Dosimetry

Six types of radiotherapy were used to treat 212 children: orthovoltage in 110, cobalt-60 in 70, a megavoltage linear accelerator in 23, a betatron in 15, electrons in 5, and brachytherapy in 10. Twenty-one children were treated with more than one method. Individual dosimetry was determined for all cases and controls by one of us (M.S.), with adjustment for age at exposure and variables such as height, weight, and body-surface area, as in previous studies.[21] The actual conditions of exposure were simulated on the basis of machine characteristics, field configurations, and treatment conditions, and doses to skeletal components of an anthropomorphic phantom were measured. Collimator-head leakage and radiation scatter from the different types of therapy machines were taken into account when possible.

For each case, the radiation dose to the site of the bone tumor was estimated, with adjustment for the difference in bone absorption associated with different energy beams. The location of the bone cancer in relation to the radiation fields was also determined to be inside, near (within 5 cm), or outside (>5 cm) any of the treated areas. For each control, the radiation dose to the equivalent site of the bone cancer in the matched case was calculated. When the information about radiation therapy was less than adequate (for 14 of 212 subjects), best estimates of the conditions and exposure were made by two of us (M.S. and G.J.D.), taking into account the hospital, calendar year, tumor site, age, and size of the subject at the time of irradiation.

Chemotherapy Quantification

The total exposure to alkylating agents was measured as previously described, accounting for multiple drug exposures and the amount of drug administered.[22] In brief, for each alkylating agent, the total dose received in relation to body-surface area (milligrams per square meter) was calculated for each study subject. A distribution of the doses received by all subjects was determined for each alkylating agent and then divided into thirds. Each subject was assigned a score of 0, 1, 2, or 3 for each drug, depending on whether the subject received no alkylating agent or fell into the lower, middle, or upper third of each distribution, respectively, The scores of all the alkylating agents were then added up for each subject in order to obtain an "alkylator score," which ranged from 0 to 9. Similar scores were developed for dactinomycin, vinca alkaloids, and other antimetabolites, which were the next most commonly used drugs.

Results

Cohort Study

Of the 9170 patients surviving for two or more years, 55 percent were male and 45 percent were under the age of five years (mean, seven) when the initial tumor was diagnosed. The mean calendar year of diagnosis was 1969 (range, 1936 to 1979). The distribution of the types of initial tumors was usual for childhood cancer as previously described.[14] Overall, 48 cases of bone cancer occurred, as opposed to the 0.4 expected (relative risk, 133; 95 percent confidence interval, 98 to 176). The absolute excess risk was 9.4 cases of bone cancer per 10,000 persons per year. The risk did not differ according to sex but was highest among children treated for retinoblastoma (relative risk, 999; absolute excess risk, 53.6 per 10^4 per year) or Ewing's sarcoma (relative risk, 649; absolute excess risk, 59.6 per 10^4 per year), followed by those with rhabdomyosarcoma (relative risk, 297; absolute excess risk, 20.5 per 10^4 per year). The relative risks were 127 for Wilms' tumor and 106 for Hodgkin's disease (abso-

Table 1. Observed and Expected Cases of Secondary Bone Cancer, with Relative and Absolute Excess Risks, among Children Living Two or More Years after the Diagnosis of a First Cancer.

Years since First Cancer	Patients in Cohort	Cases Observed	Cases Expected	Relative Risk*	Absolute Excess Risk†
2–4	9170	1	0.09	11	0.6
5–9	5524	23	0.15	152	10.7
10–14	2288	12	0.08	153	13.1
15–19	979	8	0.03	235	21.6
≥20	296	4	0.01	597	36.1

*All risks are statistically significant ($P<0.05$), but the confidence limits are wide because of the small numbers involved.

†Calculated as ([cases observed − cases expected]/number of person-years) × 10^4 — i.e., the number of excess cases per 10,000 persons per year.

lute excess risks, 7.3 and 9.4 per 10^4 per year, respectively). The relative risks increased significantly with the time since treatment (Table 1). The cumulative mean probability (±SE) that bone cancer would develop was 2.8±0.7 percent at 20 years after initial diagnosis for the entire cohort, 14.1±4.3 percent after retinoblastoma (Fig. 1), and 22.1±10.8 percent after Ewing's sarcoma.

Case–Control Study

Of the 64 bone sarcomas, 44 were osteosarcomas, 11 were chondrosarcomas, 3 were Ewing's sarcomas, 2 were fibrosarcomas, 2 were sarcomas not otherwise specified, 1 was malignant fibrous histiocytoma, and 1 was malignant mesenchymoma. Of the initial tumors, 22 were retinoblastomas (followed by 17 osteosarcomas and 5 other sarcomas); 8 were Ewing's sarcomas (all followed by osteosarcomas); 7 were Wilms' tumors (followed by 3 osteosarcomas and 4 other sarcomas); 6 were neuroblastomas (followed by 3 osteosarcomas and 3 chondrosarcomas); 6 were rhabdomyosarcomas (followed by 3 osteosarcomas and 3 other sarcomas); 5 were Hodgkin's disease (followed by 4 osteosarcomas and 1 Ewing's sarcoma); and 10 were other types of tumors. The 16 "referral" patients with bone cancer excluded from the cohort study had retinoblastoma (10 cases), rhabdomyosarcoma (2 cases), and Ewing's sarcoma, Wilms' tumor, soft-tissue sarcoma, and adrenal cortical carcinoma (1 case each). Of the second bone cancers, 34 percent occurred in the skull or mandible, 38 percent in the axial skeleton, and 28 percent in the long bones, in contrast to the usual distribution in this age group — 4 percent in the skull and mandible, 21 percent in the axial skeleton, and 72 percent in the long bones (Curtis R: personal communication).

Eighty-four percent of the cases and 73 percent of the controls received radiation therapy (relative risk, 2.7; 95 percent confidence interval, 1.2 to 7.7). The radiation dose to the site of the bone cancer ranged from 0 to 15,900 rad (total mean, 2690 rad; orthovoltage, 2900 rad; megavoltage, 2400 rad). Eighty-three percent of the bone cancers occurred inside the treatment field (relative risk, 41.6), 9.1 percent within 5 cm (relative risk, 7.4), and 7.3 percent more than 5 cm (relative risk, 0.3). The risk of bone cancer rose sharply with increasing radiation dose, reaching 40-fold when doses were more than 6000 rad (Table 2). The risk appeared to decrease, however, when doses exceeded 8000 rad (relative risk, 22.5). The pattern of risk in relation to radiation dose was essentially the same whether patients were treated with orthovoltage or megavoltage. The relative dose responses were also similar in patients treated for retinoblastoma and those treated for all other tumors (Table 2). An excess of cases of chondrosarcoma occurred only among patients who received more than 4000 rad to the osseous site before the age of six. The relative risk of chondrosarcoma (4.5) appeared to be lower than the risk of osteosarcoma (19.0) in the dose category of 4000 to 5999 rad, but corresponding risks were similar in the category of doses above 6000 rad (16.1 vs. 10.6). In further evaluating the latency trend shown in Table 1, we were unable to isolate an effect independent of age at the highest risk of bone-cancer development.

The relative risk of bone sarcoma after chemotherapy with alkylating agents was 4.7 (95 percent confidence interval, 1.0 to 22.3) after adjustment for radiotherapy. Among subjects who did not receive radiation therapy to the site where the bone cancer originated, the relative risk associated with alkylating agents was 4.2 (95 percent confidence interval, 2.6 to 6.6). The risk appeared to rise with increasing drug exposure whether or not radiation was given (Table 3). None of the cases in the high-dose category for alkylating agents had retinoblastoma.

Overall, 40 percent of the study subjects received

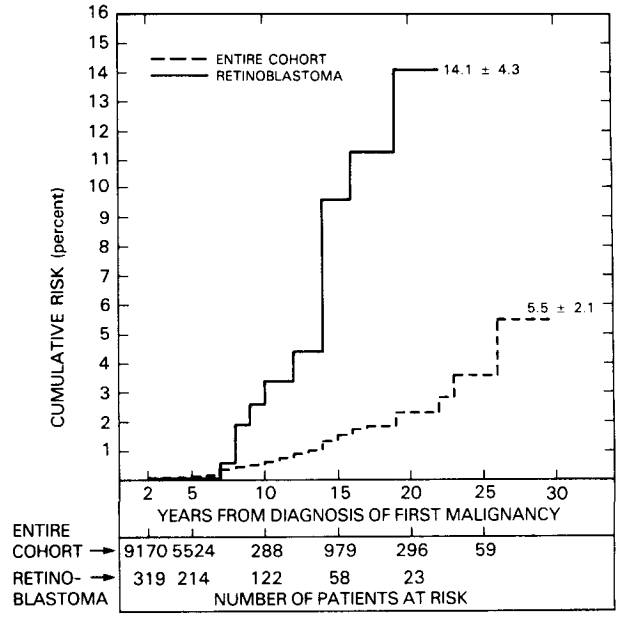

Figure 1. Cumulative Risk of Bone Cancer after Treatment for Childhood Cancer.

Cumulative risks of bone cancer after all types of childhood cancer are indicated by the broken line, and the risks of bone cancer after retinoblastoma by the solid line. Values are means ±SE.

alkylating agents; 28 percent received one drug, 10 percent two drugs, and 2 percent three or more drugs. Alkylating agents were used to treat 50 percent of the cases and 36 percent of the controls. The frequency of exposure was 29 percent for controls matched for calendar year and 39 percent for those not matched for calendar year. The interval between initial treatment with an alkylating agent and the diagnosis of bone cancer ranged from 3 to 25 years (mean, 10.3; median, 10). The drug most frequently given was cyclophosphamide, to 23 percent and 21 percent of the cases and controls, respectively (Table 4). Triethylenemelamine and chlorambucil were given twice as often to the cases (19 percent and 11 percent) as to controls (10 percent and 5 percent). The risks were not altered by excluding the now rarely used triethylenemelamine. The small number of cases exposed to specific agents precluded meaningful analysis of individual drug risks.

An increased risk of bone cancer did not appear to be associated with other drugs used for treatment of the first cancers, including dactinomycin, anthracyclines, vinca alkaloids, and other antimetabolites (Table 4). Dactinomycin did not decrease the risk (adjusted relative risk, 2.9; 95 percent confidence interval, 0.3 to 8.7). Adjustment for the use of dactinomycin also did not appreciably change the risks associated with alkylating agents or radiation.

Discussion

This multicenter study revealed an increased risk of bone cancer (133-fold) after childhood cancer, mainly due to the use of radiation therapy and chemotherapy with alkylating agents. An excess of cases of bone sarcoma was found after treatment with alkylating agents, with or without radiation to the affected site.

Table 2. Matched Relative Risk of Bone Cancer According to Type of First Cancer and Radiation Dose at the Site of Bone Cancer, Adjusted for Alkylating-Agent Treatment.

	Radiation Dose (rad)					
	0	*<1000*	*1000–2999*	*3000–3999*	*4000–5999*	*≥6000*
All types of cancers						
No. of cases	10	9	6	11	15	13
No. of controls*	51	70	30	18	23	12
Relative risk†	1.0‡	0.6	6.0	16.9	21.2	38.3
	0		*<1000*	*1000–3999*		*≥4000*
Retinoblastoma						
No. of cases	4		4	7		7
No. of controls	25		15	14		11
Relative risk†	1.0‡		1.3	12.7		19.4
All other types						
No. of cases	6		5	10		21
No. of controls	26		55	34		24
Relative risk†	1.0‡		0.2	12.0		28.8

*Five controls for whom the radiation dose to the site could not be estimated have been excluded from the analysis in this table.

†Risks for radiation dose above 1000 rad are statistically significant ($P<0.05$).

‡Referent category.

Table 3. Matched Relative Risk of Bone Sarcoma, According to Radiation Dose and Alkylator Score.

Radiation Dose	Alkylator Score		
	0	*1 or 2*	*≥3*
None			
Relative risk	1.0*	4.8	8.5†
No. cases:controls	6:44	1:4	3:3
<1000 rad			
Relative risk	1.3	0.4	1.3
No. cases:controls	5:43	1:13	3:14
≥1000 rad			
Relative risk	37.4‡	14.2‡	59.2‡
No. cases:controls	21:45	11:26	13:12

*Referent category.

†Trend in alkylator score in subjects not exposed to radiation, $P = 0.05$.

‡$P<0.05$.

The risks increased with greater amounts of chemotherapy, and were not confounded by the high rate of "spontaneous" bone sarcomas associated with genetic retinoblastoma.[6] The small group of patients who received alkylating agents without radiation therapy to the osseous site contained only one patient who had retinoblastoma, and the group given high doses of alkylators and radiation therapy contained none. The risks associated with chemotherapy were evaluated in all follow-up intervals and reached 8.5 in a small group receiving the highest dose of chemotherapeutic drugs. It is noteworthy that although chemical agents, independent of radiation exposure, have not been linked to bone cancer, two studies of retinoblastoma and Ewing's sarcoma have suggested that cyclophosphamide may potentiate the effect of radiotherapy in the development of second osteosarcomas,[8,11] and procarbazine has been reported to induce osteosarcomas in nonhuman primates.[23]

Our study also provided an opportunity to quantify the risk of bone sarcoma according to the estimated dose of radiation therapy to the bone, whereas previous studies were of a more descriptive nature.[2-12] No increased risk was associated with doses of less than 1000 rad to the osseous site, but the risk increased to 38.3 with 6000 rad or more. The overall increase in relative risk per rad was only 0.06 percent. Radiogenic bone sarcoma thus appears to be a high-dose effect following external beam exposure. No excess risk has been found among survivors of the atomic bombing of Japan,[2] and the risk reported to follow low-dose radiotherapy for tinea capitis was based on small numbers of cases.[13] The decrease in risk after the highest doses may have been due to chance or possibly to a cell-killing phenomenon, as postulated to explain the low risk of leukemia after radiotherapy for cervical cancer.[24]

It has been suggested that the level of risk of second tumors may be lower in patients treated with megavoltage than in those treated with orthovoltage.[25] When the types of radiotherapy were separated into categories of orthovoltage and megavoltage, including therapy with cobalt-60, the patterns of risk according

Table 4. Distribution of Chemotherapy Agents Given to the Study Groups.

DRUG	CASES	CONTROLS
	no. of subjects (percent)*	
Any alkylating agent	32 (50)	75 (36)
Cyclophosphamide	15 (23)	44 (21)
Triethylenemelamine	12 (19)	21 (10)
Chlorambucil	7 (11)	10 (5)
Procarbazine	4 (6)	8 (4)
Mechlorethamine	3 (5)	10 (5)
Melphalan	2 (3)	2 (1)
Nitrosoureas	2 (3)	1 (0.5)
Other alkylating agent	4 (6)	7 (3)
Dactinomycin	10 (16)	40 (19)
Vinca alkaloids	14 (22)	43 (21)
Antimetabolites	8 (13)	28 (13)
Anthracyclines	3 (5)	5 (2)

*Numbers do not add up to the total because of the use of multiple drugs.

to the total dose to the bone site were essentially the same. Eight of the nine children receiving more than 8000 rad, however, had been treated with orthovoltage. We were unable to evaluate the specific types of megavoltage exposure because the numbers of subjects were small.

Previous studies of heritable retinoblastoma have shown a genetic influence on the incidence of second bone tumors but no relation to radiation dose.[6] To evaluate this issue in our study, we matched cases and controls for bilateral retinoblastoma in an effort to factor out the genetic component and examine the treatment effect. The risk of bone cancer clearly increased with increasing radiation dose, yet the relative risks in each dose category were very similar for retinoblastomas and all other cancers. In contrast, the cumulative risk of bone cancer was higher for retinoblastoma (14 percent at 20 years) than other cancers. This figure is lower than the 50 percent cumulative risk reported by Abramson et al., but their study considered only bilateral or familial retinoblastoma.[6] Thus, although familial retinoblastoma is associated with a greater inherent risk that bone sarcomas will develop (with both tumors showing chromosomal alterations[26] involving 13q14), in our study the relative responses to radiation exposure were no different for patients with retinoblastoma than for those with other tumors. It is interesting that among the six cases of bone cancer occurring in patients not receiving alkylating agents or radiation therapy, three cancers were retinoblastoma and three were soft-tissue sarcomas, which may be associated with a genetic predisposition to bone sarcomas.[27,28] Since only 0.4 case of bone cancer was expected in the entire cohort, it seems likely that heritable factors contribute to constellations of multiple childhood cancers, including bone sarcomas.

The risk of bone cancer rose significantly with the time elapsed since initial treatment, up through 20 years. Although this pattern is consistent with the distribution of risk over time that has been reported for various radiation-induced solid tumors, it differs from the pattern in a study of radiogenic bone cancers, in which a wave-like response resembled that for leukemia.[29,30] This earlier investigation, however, was performed mainly in subjects given an injection of a short-lived radioisotope of radium.[29,30] Thus, the temporal patterns of radiogenic bone cancer may be influenced by the type of radiation and by age at exposure. Treatment effects may also contribute to the variation in the bone-cancer risk associated with the histology of the initial tumor. Thus, the very high risks after Ewing's sarcoma and rhabdomyosarcoma seem to be related to relatively high-dose radiation and alkylating agents, but genetic susceptibility may also play a part in these tumors, as in retinoblastoma.

The results of our study should be viewed in the light of three methodologic concerns. First, although the radiation dose to the site of the bone tumor was calculated for 95 percent of the subjects, for 5 percent the information about treatment or location was inadequate and best estimates were made. Excluding these subjects from the analysis, however, did not appreciably alter the risks associated with radiation. Second, the alkylator score was developed primarily as a means to evaluate the doses of multiple drugs and is less useful when few drugs are administered or when drugs differ in their potential for carcinogenesis.[31] Third, the potential for bias raised by including cases not originally treated at the participating hospitals was evaluated, but no significant difference in risk estimates was found when the referral cases were excluded.

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REFERENCES

1. Martland HS. Occupational poisoning in manufacture of luminous watch dials. JAMA 1929; 92:466-73.
2. Fraumeni JF Jr, Boice JD Jr. Bone. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer epidemiology and prevention. Philadelphia: W.B. Saunders, 1982:814-26.
3. Cahan WG, Woodard HQ, Higinbotham NL, Stewart AW, Coley BL. Sarcoma arising in irradiated bone: report of eleven cases. Cancer 1948; 1:3-29.
4. Huvos AG, Woodard HQ, Cahan WG, et al. Postradiation osteogenic sarcoma of bone and soft tissues: a clinicopathologic study of 66 patients. Cancer 1985; 55:1244-55.
5. Meadows AT, Baum E, Fossati-Bellani F, et al. Second malignant neoplasms in children: an update from the Late Effects Study Group. J Clin Oncol 1985; 3:532-8.
6. Abramson DH, Ellsworth RM, Kitchin FD, Tung G. Second nonocular tumors in retinoblastoma survivors: Are they radiation-induced? Ophthalmology 1984; 91:1351-5.
7. Sagerman RH, Cassady JR, Tretter P, Ellsworth RM. Radiation induced neoplasia following external beam therapy for children with retinoblastoma. Am J Roentgenol Radium Ther Nucl Med 1969; 105:529-35.
8. Strong LC, Herson J, Osborne BM, Sutow WW. Risk of radiation-related subsequent malignant tumors in survivors of Ewing's sarcoma. JNCI 1979; 62:1401-6.
9. Greene MH, Glaubiger DL, Meade GD, Fraumeni JF Jr. Subsequent cancer in patients with Ewing's sarcoma. Cancer Treat Rep 1979; 63:2043-6.
10. Li FP. Second malignant tumors after cancer in childhood. Cancer 1977; 40:1899-902.
11. Draper GJ, Sanders BM, Kingston JE. Second primary neoplasms in patients with retinoblastoma. Br J Cancer 1986; 53:661-71.
12. Meadows AT, Strong LC, Li FP, et al. Bone sarcoma as a second malignant neoplasm in children: influence of radiation and genetic predisposition. Cancer 1980; 46:2603-6.

13. Ron E, Modan B, Boice JD Jr. Mortality from cancer and other causes following radiotherapy for ringworm of the scalp. Am J Epidemiol (in press).
14. Tucker MA, Meadows AT, Boice JD Jr, Hoover RN, Fraumeni JF Jr. Cancer risk following treatment of childhood cancer. In: Boice JD Jr, Fraumeni JF Jr, eds. Radiation carcinogenesis: epidemiology and biological significance. New York: Raven Press, 1984:211-24.
15. Monson RR. Analysis of relative survival and proportional mortality. Comput Biomed Res 1974; 7:325-32.
16. Heston JF, Kelly JAB, Meigs JW, Flannery JT, Cusano MM, Young JL Jr. Forty-five years of cancer incidence in Connecticut: 1935–79. Natl Cancer Inst Monogr 1986; 70:333.
17. Waterhouse J, Muir C, Correa P, Powell J, eds. Cancer incidence in five continents. Vol. III. Lyon, France: International Agency for Research on Cancer, 1976.
18. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-81.
19. Lubin JH. A computer program for the analysis of matched case-control studies. Comput Biomed Res 1981; 14:138-43.
20. Rothman KJ, Boice JD Jr. Epidemiologic analysis with a programmable calculator. Boston: Epidemiology Resources, 1982.
21. Stovall M. Organ doses from radiotherapy of cancer of the uterine cervix. In: Day NE, Boice JD Jr, eds. Second cancer in relation to radiation treatment for cervical cancer: results of a cancer registry collaboration. New York: Oxford University Press, 1984:131-5.
22. Tucker MA, Meadows AT, Boice JD Jr, et al. Leukemia after therapy with alkylating agents for childhood cancer. JNCI 1987; 78:459-64.
23. Sieber SM, Correa P, Dalgard DW, Adamson RH. Carcinogenic and other adverse effects of procarbazine in nonhuman primates. Cancer Res 1978; 38:2125-34.
24. Boice JD Jr, Day NE, Andersen A, et al. Second cancers following radiation treatment for cervical cancer: an international collaboration among cancer registries. JNCI 1985; 74:955-75.
25. Potish RA, Dehner LP, Haselow RE, Kim TH, Levitt SH, Nesbit M. The incidence of second neoplasms following megavoltage radiation for pediatric tumors. Cancer 1985; 56:1534-7.
26. Hansen MF, Koufos A, Gallie BL, et al. Osteosarcoma and retinoblastoma: a shared chromosomal mechanism revealing recessive predisposition. Proc Natl Acad Sci USA 1985; 82:6216-20.
27. Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms: A familial syndrome? Ann Intern Med 1969; 71:747-52.
28. Williams WR, Strong LC, Norsted TL. Genetic epidemiology of childhood soft tissue sarcoma (STS). Proc Am Assoc Cancer Res 1985; 26:208. abstract.
29. Mays CW, Spiess H. Bone sarcomas in patients given radium-224. In: Boice JD Jr, Fraumeni JF Jr, eds. Radiation carcinogenesis: epidemiology and biological significance. New York: Raven Press, 1984:241-52.
30. Committee on the Biological Effects of Ionizing Radiations. The effects on populations of exposure to low levels of ionizing radiation: 1980. Washington, D.C.: National Academy Press, 1980.
31. Greene MH, Harris EL, Gershenson DM, et al. Melphalan may be a more potent leukemogen than cyclophosphamide. Ann Intern Med 1986; 105: 360-7.

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